REMARKS

Claims 1 to 52 are currently pending in the application. Claims 1 to 10 and 49 to 52 stand rejected, and claims 11 to 48 are objected to. Claims 1 to 4, 6 to 10, and 49 to 52 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1 to 5, 7 to 10, and 49 to 52 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 11 to 48 are objected to as being dependent upon a rejected base claim but are otherwise allowable. Applicants are herein amending claims 1, 17, and 49. Upon entry of this amendment, claims 1 to 52 will be pending.

Amendments to Claims

Applicants are herein amending claim 1 to delete "dihydrobenzodioxinyl" from among the choices provided for the "Ar" substituent. Applicants are herein amending claim 17 to present the claim in independent format. Applicants are also herein amending claim 49 to remove "cocaine addiction" from among the pathologies listed in the claimed method.

Applicants respectfully submit that no new matter is introduced by the amendments to the claims and such amendments are fully supported by the specification and claims, as originally filed.

Applicants submit that the amendments to the claims do not introduce new matter and are fully supported by the specification and claims, as originally filed. Applicants request the entry of the amendment under 37 C.F.R. § 1.116(b) because the amendments to the claims either cancel claims, comply with requirements of form expressly set forth in a previous Office Action, or present the rejected claims in better form for consideration on appeal.

Rejection under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1 to 4, 6 to 10, and 49 to 52 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In order to expedite resolution of this matter, applicants are herein amending claim 1 to delete dihydrobenzodioxinyl as a choice for "Ar", and are herein amending claim 17 to convert that claim from dependent to independent format. Applicants submit that these amendments render moot the rejection for lack of written description. Accordingly, applicants respectfully request withdrawal of claims 1 to 4, 6 to 10, and 49 to 52 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1 to 5, 7 to 10, and 49 to 52 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

Applicants respectfully submit that the Office has again mischaracterized its burden to demonstrate that the rejected claims are not, as alleged, properly enabled. The Office repeats the generalized assertions originally presented in the Office Action mailed 02/09/2005, *viz.*, that the pharmaceutical art is generally less predictable than other arts and the subjective belief that the genus of compounds of formula I could not have the selective serotonin reuptake inhibition and antagonism at the $5HT_{1A}$ receptor. However, the Office does not provide objective, technical reasons or any evidence why the rejected claims would not be viewed by those skilled in the art at the time the invention was made as properly enabled. Although would be the case that *in the face of objective evidence* that the claimed genus of compounds do not have SSRI/$5HT_{1A}$ antagonist activity, "merely asserting" the contrary would not automatically avoid an enablement rejection, the stage wherein applicants are required to come forth with evidence to rebut an objective showing of non-enablement has not yet been reached. This is because, at the outset of the patent examination process, it is the Office that bears the initial burden of proof with respect to non-enablement, and the Office

has not met this burden. *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971) ("it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to . . . back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.").

Generalized citation to case law and conclusory commentary therewith have not allowed the Office to overcome the initial hurdle of providing objective evidence of failure to meet the requirements of 35 U.S.C. § 112, first paragraph. For example, it is true that the case of *In re Fisher*, 427 F.2d 833 (C.C.P.A. 1970), cited by the Office, does provide that in less predictable arts such as those involving "chemical reactions and physiological activity" that the scope of enablement is inversely proportionally more demanding; applicants were cognizant of this mandate when applicants drafted the instant specification to include three art-recognized assays for SSRI and $5HT_{1A}$ activity and provided a claim scope that is objectively reasonable in light of the specification and the knowledge of those skilled in the art. Furthermore, the facts of *In re Fisher* are distinguishable from those at issue here, as applicants in that case had presented a claim that included an "open-ended recitation" directed to chemical compositions having potencies in excess of 1.11 "International Units of ACTH activity per milligram" even though the specification only disclosed products having potencies from 1.11 to 2.3 International Units. *See* 427 F.2d at 839. In the instant case, in contrast, applicants have presented carefully circumscribed claims directed to compounds that provide SSRI and $5HT_{1A}$ antagonist activity and have used assays that are widely accepted among those skilled in the art for demonstrating that representative embodiments possess the described physiological activity, as compared with attempting to claim "future [and as yet unidentified] compositions having potencies far in excess of those obtainable from the teachings plus ordinary skill." *See id.* Thus, while the general proposition of *In re Fisher* – which delineates the required scope of enablement in less predictable arts – is correct, the outcome of the case itself is factually distinguishable from the instant situation, where applicants do not attempt to claim compounds that would not be recognized by those skilled in the art as objectively lacking SSRI/$5HT_{1A}$ activity. Neither has the Office provided an objectively reasonable basis to support its position to the contrary.

The Office has also submitted that applicants' analysis of the enablement requirement is not consistent with the MPEP, namely § 2164.05(a), presumably being of the view that because the disclosed core structure was not known in the prior art, applicants' statement that the skilled artisan would accept the disclosed model as reasonably correlating to the claimed effects cannot be relied upon "to contribute to the enablement issue." *See* Office Action of 7/26/2005 at 3. But applicants' previous argument refers to the fact that, at the time the instant application was filed, it was widely recognized among those skilled in the art that the assay for determining the disclosed compounds' affinity for the 5HT transporter, the assay for the $5HT_{1A}$ receptor, and the assay for antagonist activity at the $5HT_{1A}$ receptor, as well as the synthesis schemes, dosage forms and dosage levels, and dual SSRI/$5HT_{1A}$ activity data, reasonably correlate to the effects claimed in claims 1 to 5, 7 to 10, and 49 to 52 (*see* May 5, 2005 Reply at 14-15), not that compounds having the disclosed X-Y core structure are art-recognized as correlating to a particular effect. Thus, applicants have submitted that the state of the art with respect to the former aspects of the instant disclosure may be used to conclude that the rejected claims are enabling as of the filing date. Contrary to the suggestion of the Office, applicants have not asserted that the knowledge of those skilled in the art at the time the instant application was filed included specific facts about compounds having the disclosed X-Y core structure. Although it is the Office's burden to do so in light of the applicants' disclosure and argument, the Office does not present evidence that those skilled in the art would not consider the present disclosure to be enabling as of the filing date, and so a *prima facie* case of non-enablement has not been established. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (C.C.P.A. 1971) ("it is incumbent upon the Patent Office, when ever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure...Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.") (emphasis in original).

As provided in the communication of May 5, 2005, applicants therefore respectfully submit that because the non-enablement rejection is not supported by sufficient evidence that the compounds of Formula I and methods of their use cannot be made and used in the manner described in the specification without undue experimentation, there is not a reasonable basis

for rejecting the claims. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 to 5, 7 to 10, and 49 to 52 under 35 U.S.C. § 112, first paragraph, for alleged non-enablement.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claim 49 stands rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Although the Office Action suggests otherwise, at the time the instant application was filed, there was documented recognition by those skilled in the art of the efficacy of SSRI drug therapy for treating the pathologies specified claim 49 of the present application. As detailed below, there is voluminous confirmation by those skilled in the art that selective serotonin reuptake inhibition, when effected through therapeutic administration of pharmacological agents, can benefit patients that suffer from the medical conditions specified in claim 49. To expedite the resolution of the current rejection, applicants are herein amending claim 49 to remove cocaine addiction from among the pathologies listed in the claimed method.

For example, SSRI compounds like sertraline and other SSRIs have been shown to have a broad range of efficacy in treatment of post-traumatic stress disorder (PTSD) and also alcoholism (*see* Brady KT *et al.*, "Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence," *J. Clin. Psychiatry* 56:502-5 (**1995**); attached); paroxetine has also been shown to represent effective treatment for PTSD (*see* Wagstaff AJ, *et al.*, "Paroxetine: an update of its use in psychiatric disorders in adults," *Drugs,* 62(4):655-703. Review (**2002**)); fluoxetine has been demonstrated an effective treatment for attention deficit/hyperactivity disorder (*see* Kafka MP, Hennen, J., "Psychostimulant augmentation during treatment with selective serotonin reuptake inhibitors in men with paraphilias and paraphilia-related disorders: a case series," *J. Clin. Psychiatry,* 61(9):664-70 (**2000**); attached); escitalopram oxalate (*e.g.,* Lexapro®) has been proven efficacious and is FDA approved for treatment of generalized anxiety disorder (*see* Lexapro® package insert, page 3; attached); Boyer WF, "Potential indications for the selective serotonin reuptake inhibitors," *Int. Clin. Psychopharmacol.* 6 Suppl. 5:5-12 (**1992**) (attached) demonstrates that the common

SSRI side effect of decreased appetite and subsequent weight loss appears to be most pronounced in obese patients and may be a useful effect as an adjunct to diet and exercise in cases of severe obesity; Boyer also reports that fluoxetine is an effective treatment for anorexia nervosa, an eating disorder, as well as premenstrual dysphoric disorder; fluoxetine (*e.g.,* Prozac®) is also indicated for treatment of bulimia nervosa, another eating disorder (*see* Prozac® package insert, page 8, attached); venlafaxine (*e.g.,* Effexor®), paroxetine (*e.g.,* Paxil®), sertraline (*e.g.,* Zoloft®), and fluoxetine (*e.g.,* Prozac®) have all been shown effective in treatment of vasomotor flushing (*see, e.g.*, Stearns V., *et al.*, "Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial," *JAMA*, 289(21):2827-34 (**2003**); *see also* Loprinzi, CL, *et al.*, "Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial," *Lancet*, 356(9247):2059-63 (**2000**); both attached); fluoxetine has furthermore been demonstrated efficacious in treatment of alcoholism (*see* Janiri L, *et al.*, "*Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics*," *Int. Clin. Psychopharmacol.* 11:109-17 (**1996**); attached); and, paroxetine, citalopram, and other SSRIs have been used to effectively treat certain forms of sexual dysfunction. *See* McMahon CG and Touma K, "Treatment of premature ejaculation with paroxetine hydrochloride," *Int. J. Impot. Res.,* 11(5):241-245; discussion 246 (**1999**); Atmaca M, *et al.*, "The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study," *Int. J. Impot. Res.*, 14(6):502-5 (**2002**), both attached.

Therefore, applicants submit that at the time the instant invention was filed, persons skilled in the art widely recognize the nexus between treatment of the specified medical conditions and the mediation of serotonin uptake via treatment with compounds identified as possessing SSRI functionality.

Furthermore, the interplay between the serotonin transporter (SERT) and the $5HT_{1A}$ receptor has been characterized by those skilled in the art, and the instant invention specifically utilizes this interplay to effect enhanced treatment for specified medical conditions. It is well-documented that reduction of negative feedback and augmentation of the serotonin reuptake mechanism can be effected by coadministration of $5HT_{1A}$ antagonists.

See Perez, *et al.* **(1997)** (cited in IDS mailed January 27, 2004, as considered by Examiner February 7, 2005); *see also* Perez V, Puigdemont D, Gilaberte I, Alvarez E, Artigas F, "Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors," *J. Clin. Psychopharmacol.* **(2001)** Feb;21(1):36-45; attached. Thus, it is well known in the art that selective serotonin reuptake inhibition, and enhancements thereof (*e.g.,* via $5HT_{1A}$ antagonism), can provide the basis for particularized therapeutic treatment as recited in claim 49.

Accordingly, applicants respectfully request reconsideration of the rejection of claim 49 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants submit that the claim, as amended, is in proper condition for allowance, and that claims 50 and 51, which depend from claim 49, are also in condition for allowance.

Conclusions

In view of the above, applicants respectfully request:

- entry of the amendments to claims 1, 17, and 49;
- reconsideration and withdrawal of the rejection of claims 1 to 4, 6 to 10, and 49 to 52 under 35 U.S.C. § 112, first paragraph (written description);
- reconsideration and withdrawal of the objection to claims 11 to 48;
- reconsideration and withdrawal of the rejection of claims 1 to 5, 7 to 10, and 49 to 52 under 35 U.S.C. § 112, first paragraph (enablement); and,
- reconsideration and withdrawal of the rejection of claims 49 to 52 under 35 U.S.C. § 112, first paragraph (enablement).

If the Examiner is of a contrary view, the Examiner is requested to contact the undersigned attorney at (404) 459-5642.

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